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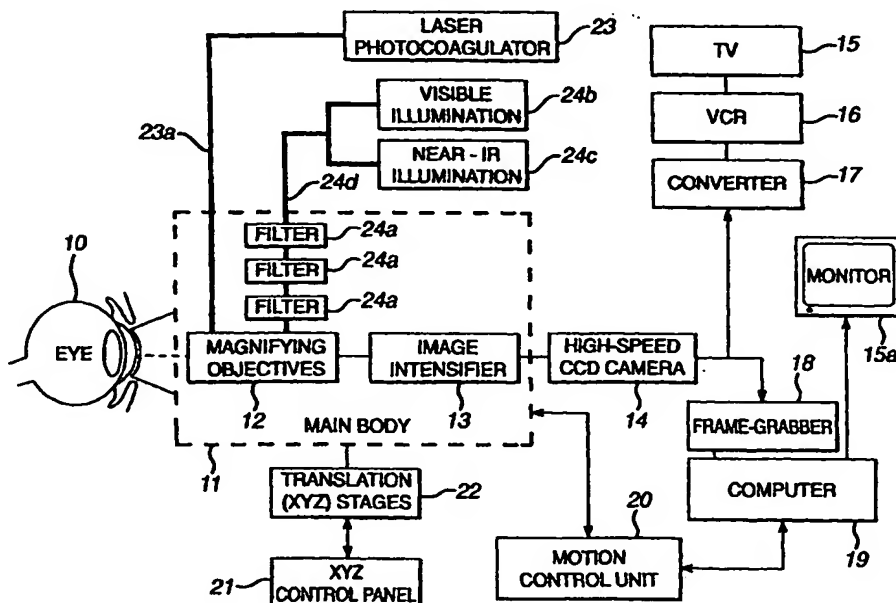
(57) Abstract

A method and apparatus for detecting and treating diseases of a type associated with the growth of new blood vessels (neovascularization) in choroidal or subretinal layers of the eye and which can be used for more accurately locating a feeder vessel to the neovascularization and for blocking such a feeder vessel by photocoagulation with a laser.

1

METHOD AND APPARATUS FOR TREATING NEOVASCULARIZATION

The present invention relates to a method and apparatus for
5   detecting and treating diseases of a type associated with
the growth of new blood vessels (neovascularization) in
choroidal or subretinal layers of the eye.   More
particularly, the invention can be used for more accurately
locating a feeder vessel to the neovascularization and for
10 blocking such a feeder vessel by photocoagulation with a
laser.

Age-related Macular Degeneration (AMD) is a chronic disease
affecting primarily the choriocapillaris, Bruch's membrane
15 and the Retinal Pigment Epithelium (RPE). It is the most
common cause of legal, irreversible blindness in patients
aged 65 and over in the US, Canada, England, Wales,
Scotland and Australia. Although the average age of
patients when they lose central vision in their first eye
20 is 65 years, some patients develop evidence of the disease
in their fourth or fifth decade of life.

Approximately 10% to 15% of patients manifest the exudative
form of the disease. Exudative AMD accounted for 79% of
25 legally blind eyes. The disease is bilateral with
accumulating chances of approximately 10% to 15% per annum
of developing the blinding disorder in the fellow eye. The
recurrence rate of a treated neo-vascular membrane has been
estimated to be 50% within 18 months, but more recent
30 research with Photo-Dynamic Therapy (PDT) has indicated a
recurrence rate of 50% within 12 weeks from the last
treatment.

The hallmark of the exudative form of the disease is a
35 Choroidal Neo-Vascular Membrane (CNVM) that grows beneath
the retina or the RPE in the foveal-macular region. This
CNVM leaks and bleeds evoking a scaring reaction that

eventually results in the scaring of the affected area with consequential blindness. Histopathology of these CNVMs revealed that the vast majority of the membranes are nourished by a few (1 to 3) feeder vessels only. This means that only a few "vascular bridges" connect the origin of the CNVM (in the choroid) to the new location beneath the retina or the RPE.

The currently available treatment, as recommended by the Macular Photocoagulation Study (MPS) is massive destruction of the membrane with an appropriate laser. Unfortunately, most of the membranes are sub-foveal when discovered and such a treatment modality leads to the complete destruction of all tissues - CNVM and retinal - within the treated area. It has been suggested that focusing on feeder vessel destruction will minimise the collateral damage caused by massive tissue ablation. The major problem with this feeder treatment is the limited patient eligibility because of the difficulty in identifying feeder vessels. (Ref: F Shiraga, et al. OPHTHALMOLOGY, 105#4, 662-669, Apr 1998.)

Thus existing techniques for the treatment of AMD can not treat the disease satisfactorily. The known techniques routinely damage blood vessels and tissues unrelated to the disease or the disease-causing areas. Essentially, these techniques lack the ability to locate and destroy feeder vessels to the neovascularization with sufficient accuracy.

One object of the present invention to provide a method of treatment of neovascularization that overcomes or at least ameliorates the disadvantages identified.

Another object of the present invention to provide apparatus which can be used for more accurate determination of the location of feeder vessels to the neovascularization.

Accordingly, a first aspect of the invention provides a method of treating neovascularization in the eye of patient comprising:-

5   (i) introducing a detectable marker into the circulation of the patient at a point remote from the eye;
(ii) observing a region of suspected neovascularization in the eye after introducing the marker;
(iii) detecting the location of the onset of the marker
10   into the region in order to determine the location of a feeder vessel to the region of neovascularization or an anomaly in the retinal pigment epithelium; and
(iv) photocoagulating the feeder vessel to prevent it from feeding blood to the neovascularization.

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The invention also provides apparatus for examination of neovascularization in an eye of a patient, comprising:-

a light source for exciting a dye introduced into the
20   circulation of the patient;
an image generator for generating an image of a region of the eye under examination; and
an image recorder for recording a plurality of images of the region.

25

WO-A-98/46122 describes one form of apparatus which, together with the modifications and/or improvements described herein, can be used in preferred embodiments of the invention. Where applicable, the contents of
30   WO-A-98/46122 are incorporated herein by reference.

Typically, the detectable marker is a fluorescent dye, the region is illuminated by radiation that excites the dye and the first appearance of the dye in the region is detected
35   as an increase in brightness by a predetermined amount above background levels. In an example of the invention in use, a video image of the region is monitored for the first

appearance of the dye. Initially, the image is dark, indicating that no fluorescent dye has entered a blood vessel contributing to the image. As soon as the dye does enter the field of the image, it is visible as an area of

5   increased brightness and its position and course is readily seen and recorded.

As the time between the first appearance of the marker with just one or a small number of areas of brightness in the

10   image and the filling of most of the image with the dye is usually very short, of the order of fractions of a second, it is preferred that the region is observed by recording a succession of images of the region using an image recorder and subsequently examining the recorded images to identify

15   the location of a blood vessel feeding blood into the region. This enables images to be stored for later examination. A suitable rate of capture of images is at least 30 per second, though it is preferred that the rate is at least 45 per second, and higher rates such as 60 per

20   second and greater will tend to give improved identification of feeder blood vessel location.

In an embodiment of the invention, the recording of images of the region is triggered by triggering means associated

25   with the image recorder and sensitive to an increase of the marker in the region. The trigger can be set so as to trigger image capture when the brightness level rises above the average background level plus a predetermined amount. This may be initially set at a level of, say, 10 per cent

30   but is usually optimised empirically. Computer memory usage for image storage is relatively high, and thus this embodiment is of benefit in that unnecessary storage of image prior to the first appearance of the dye in the region is reduced and may even be totally avoided.

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In an alternative embodiment of the invention, the recording of images of the region is immediately initiated

at the injection of the marker(s). In this embodiment, the total recording time must be of ample length so as to record the earliest appearance of the marker in the region (and even into later periods when the marker accumulates

5   and fills in the region). The total recording time should preferably be 30 seconds or more for storing images at a rate of 30 full frames per second, minimum. It is even more preferable to have a total recording time of 30 seconds or more for storing images at a rate of 60 full frames per

10   second or more. In this embodiment, no triggering or empirically determined threshold is required as ample recording media (memory) is provided to store the entire captured sequence of images. Thus, no particular sensitiveness to the increase of the marker is required.

15
     In a further embodiment of the invention, the method additionally comprises introducing a second detectable marker into the circulation of the patient, and detecting the location of the second detectable marker in the region

20   so as to determine the position of the blood vessel walls in the region. This second marker is generally used to identify blood vessels throughout the region, so as to build up a map or network of the vasculature especially the blood vessel walls of the feeder vessels suspected of

25   causing or contributing to the disease. This second detectable marker can be used in real time, not needing the fast image capture of the first marker. In use, the image or images showing the location of the first appearance of the first detectable marker into the region are compared

30   with the position of the blood vessel walls located by the second detectable marker, such as by overlaying one image onto the other, so that it is possible to determine the location of a blood vessel feeding blood into the region. This introduces further accuracy into the identification of

35   the feeders, or, a confirmation of the locations of suspected feeder blood vessels. For example, if the CNVM is under examination, the stained blood vessel walls can be

compared with the positions of the first fillings of the region and only those overlapping areas are to be considered as feeder vessels to be treated.

5 The treatment to be applied may be by conventional laser photocoagulation. In addition, it is a preferred embodiment of the invention that the treatment is carried out using a laser having the same absorption wave band of the second detectable marker.

10

In apparatus embodying the invention, an image generator generates an image of a region of the eye under examination; and an image recorder records a plurality of image frames of the region. The image recorder preferably

15 records images at a rate of at least 30 frames per second, or faster, and for a total recording time of not less that 30 seconds (at whichever rate being used).

In a preferred embodiment of the invention, the apparatus

20 the further comprises a trigger means associated with the image recorder and sensitive to an increase of the marker in the region, wherein it triggers image recording in response to an increase of the marker in the region above a predetermined level.

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Thus using the method of the invention, in order to locate a target, it is not necessary to see the target clearly or sharply, as long as the target is marked or contrasted or is easily differentiated from the background by a visible

30 marker, e.g. a dye.

Embodiments of the invention will now be described with reference to the accompanying drawings in which:

35 Fig.1 is a schematic diagram of opthalmalogical apparatus for examining and treating the eye.

Figs.2 and 3 schematically illustrate parts of the eye.

Figs.4a-4c and 5a-5e show image frame sequences and the spread of a marker into a feeder region of a
5   neovascularization.

Referring first to Fig.2, this shows schematically a section through the eye and illustrates the lens 1 of the pupil region, the schlera 2, and retina 3. The section
10   also shows the choroid 4, pigment epithelium 5 and fovea 6. Referring next to Figs. 3a-3b, these schematically illustrate a magnified portion of the eye including the RPE (retinal pigment epithelium) 5, shown as a layer. Figs. 3a-3b are shown as a sequence to illustrate the anatomy and
15   growth of the CNVM (choroidal neo-vascular membrane). This includes the RPE, which is furthest from the cornea, protruding feeders and the CNVM itself which grows into the retina or pushes the RPE upwards causing a "bump" in the retina (as depicted by the sequence of Figs. 3a-3b). The
20   invention enables the location of a feeder 7 to the neovascularization to be more accurately determined (compared with the techniques described in WO-A-98/46122). For example, after introducing a marker into the patient's circulatory system, the marker can be detected in the
25   foveal-macular region of the patient's eye when it starts to fill the feeder, whereby the location of the feeder 7 to the neovascularization can be accurately determined so that a laser can be subsequently used to cause photocoagulation, thereby blocking the feeder. In carrying out this method,
30   a high speed CCD camera is coupled to an image intensifier which in turn is coupled to the optical system that is focused on a region where a feeder 7 is suspected. Whilst this does not essentially require confocal paths, they would be useful for focusing on a thin slice. For example,
35   if such a slice were thinner than the gap between the choroid or RPE and the CNVM, the optical system can be focused on feeders suspected to be located somewhere

8

between the top and bottom of the "bump", while the RPE and CNVM would remain out of focus, i.e. blurred out. However, the confocal system is not essential in every case. The choroid cannot be seen because it is shielded by the RPE

5   (which is opaque to visible light) and to see the choroidal vasculature, ICG (in the IR) and the confocal capability to focus above the choriocapillaris can be employed to detect the lesion protruding into the RPE, the marker being a substance such as fluoroscein (in the visible blue/green).

10 Whilst fluoroscein filling of the choroid is not visible (because of the RPE), unless there are breaks in the RPE (due to the feeders/CNVM of a disease, or just "window defects", feeder filling will be seen followed by the neo-vascular network filling, by observing bright spots against

15 a dark RPE background. i.e. with focus on or about the RPE/retina. This is schematically illustrated by the sequence Figs. 4a-4c, which show respectively the start of the filling of the feeder and the subsequent filling of vessels by capturing frames of image information with the

20 high speed camera. Almost immediately after the appearance of bright spots indicating the locations of feeders, the visible retinal vascularture fills, producing a brilliant flash which drowns out all the spots. By careful selection and adjustment of timing, i.e. to ensure that sufficient

25 image frames are captured at a high enough frame speed, the captured frames show the first appearance and subsequent growth of these spots. These frames (of interest) which are taken over a very short period of time, can be subsequently examined and analysed to see how the

30 brightness of each spot develops (between the choroidal filling and the retinal flash). Confocal paths are of use because they enable narrow focusing on a layer just above the RPE and not too much into the retina. In this way, the retinal flash can be reduced or eliminated (i.e. noise

35 reduction/elimination. Then ICG and the confocal system (if needed) can be used to confirm that these spots are diseased (and not window defects in the RPE). Disease

spots are stained by ICG in the longer term (e.g. of 3-5
minutes post-injection). By then superimposing flouroscein
stills on the live, evolving ICG staining, and focusing on
the thin layer about the spot (so as not to excite the ICG,
5   which may still be coursing through the normal choroidal
and retinal vasculature - but which would be out of focus
in ·the confocal system), the disease spots can be
confirmed, targeted and treated.

10   Fast cameras and fast computers can be used to catch those
images between the invisible filling of the choroid and the
invisible filling of the retinal vessels. There is no need
for specific focusing at locations where feeders are
suspected   to   exist.   It   would   help   in   signal
15   discrimination, especially with confocal paths, but is not
necessary if frames can be captured in the intervening few
milliseconds between sequential fillings. Hence, one would
see dark, a few brightening spots and then the flash of the
retinal vessels. Referring to Fig. 1, this schematically
20   illustrates the kind of apparatus which can be used to
carry out the invention. Reference is also made to WO-A-
98/46122, for further details of the optical and other
systems which are represented schematically in Fig. 1 by
the main body 11, which includes inter alia the magnifying
25   objectives 12.   Fig. 1 shows the eye 10 positioned in front
of the lens system and further details of this will be
apparent from WO98/46122. Arranged on the image path is an
image intensifier 13 coupled to high speed CCD camera 14.
This is linked to video image generating apparatus
30   including a TV unit 15, CCR 16 and image converter 17.
Monitor 15a enables images to be viewed. Camera 14 also
has a input for a frame grabber 18 which is linked to
computer 19. Motion control unit 20 is coupled between the
main body 11 and computer 19. An XYZ control panel 21 is
35   coupled to translation (XYZ) stages 22 also coupled to the
main body 11. A laser photocoagulator 23 is connected by
means of a fibre optic light guide to the magnifying

objective lens system 12. A visible illumination source 24b and a near IR illumination source 24c are on an illumination path 24d to a filter system 24a which is coupled to the magnifying objectives 12.

Essentially, the system disclosed in WO-A-98/46122 is upgraded with more speed, more RAM, and image capturing means which enable images to be captured in the required brief time interval and with the necessary spatial resolution, so that the feeders can be identified and treated.

The distribution of the marker inside the target region, such as within a CNVM, always starts at the feeder or feeders. Consequently, the more closely temporally-spaced images are captured during the first second of the marker's entry into the CNVM, the better the chances of locating and confirming the feeders. That is, each image should be captured in as short a period as possible (i.e. high temporal resolution), and, the time elapsed between consecutively captured images should be as short as possible (i.e. high rate of capture). In addition, each image should have as high an image resolution as achievable so that details of the region can be seen. The invention may use any high speed image -capturing devices or sensors currently available to achieve improved identification of the feeder vessels.

Where triggering and threshold detection are not required, a feeder can be identified and located by the following technique.

(i) The entire captured sequence can be replayed in "slow-motion-stop- frame" so that the few (consecutive) images in which the marker first appears can be identified.

(ii) The brightening regions (or spots) in one of these images can be defined (marked out) and "registered".

(iii) A graph plotting the brightness levels (within each of the registered spots in every image in the captured

sequence) against the order of the images (in the captured sequence).

(iv) In this manner, the brightness changes (increases) with time, within each registered spot, from before the marker arrives to well after the marker has filled the spots, can be illustrated graphically. Any suitable type of graphs can be used: 2-dimensional, 3-dimensional, histogram, etc.

(v) The rise and fall of the graph of each registered spot identifies a spot as a suspected feeder, or a "window defect" in the RPE. A feeder will fill with the marker and maintain its saturated brightness. A break (in the RPE) will show the underlying flash followed by a reduction in the brightness over several seconds (hundreds of images) before the brightness level rises again in the redistribution of the bolus. Hence, feeder locations are identified.

(vi) Other anomalies (in the RPE) can be studied by this method.

It has been found that magnification is more important than resolution when searching for a feeder vessel. In preferred embodiments of the invention, an operator may trade off a decision not to pursue higher resolution to enable a better view of a feeder. Preferably, accurate destruction of the feeders should be performed immediately once they are identified, and the invention advantageously provides for these functions both to be incorporated in one instrument.

In a specific embodiment of the invention, two fluorescent dyes, ICG and fluorescein, are injected into the circulation (simultaneously or separately) as is done in any current angiographic imaging procedure. At the earliest entrance of the fluorescein into the choroidal circulation, the increase in the brightness of the background haze is detected by the instrument, which then automatically self-triggers the image acquisition. The very earliest

12

filling of the CNVM is acquired as rapidly as possible using a (digital) camera operating at a rate of 60 frames per second. The faster the image acquisition, the better the details of the earliest appearance of the dye, the

5   better the ability to locate and confirm feeder vessels. All the images acquired during this early phase are presented on the computer monitor to be studied by the instrument operator(s). The earliest images that show the entry of the fluorescein into the CNVM are isolated and

10   selectively stored as individual frames (marked or numbered or both) in the computer memory.

Image processing (software) is then used to analyse and enhance the location(s) where the fluorescein starts its

15   entry into the CNVM. While executing this procedure of analysing fluorescein early filling, the second marker, ICG, is staining the vessel walls of the CNVM. This staining process is being monitored, in real time, by the instrument operator(s). The stored image(s) of the first

20   (fluorescein) marker's early filling is recalled, made semi-transparent and then overlaid or otherwise superimposed on the real-time image of the ongoing staining of the membrane by the second marker. Only the stained vessels of the CNVM that are within the marked areas of the

25   stored early (fluorescein) filling images are to be considered as possible feeders. A (100(m laser spot of appropriate power is aimed directly at the suspected feeder(s) and the treatment mode (photocoagulation) is executed. Preferably, the laser spot size should be between

30   (50(m and (100(m to adjust to the expected cross-sections of the feeder vessels. Even more preferably, the laser spot size itself may be adjusted, in real time, by any combinations of optical and opto-mechanical means, between these limits. An aiming beam enables accurate laser shots

35   to be applied to the target(s).

The wavebands of the treatment laser used for the treatment

and the aiming are the same as that needed to excite the fluorescent marker (ICG) that stains the vessel walls of the CNVM. In this way, it is possible to combine better targeting and better treatment at lower powers due to

5   enhancement in the absorption (of laser energy) by the second marker.

The instrument itself may also include a self-tracking system that uses the large vessels at the rim of the optic

10 disc as alignment reference points in order to overcome the patient's unintentional eye movements.

The method of the invention is found to produce good results as it enables high magnification of the CNVM (while

15 compromising on resolution). This "trade-off" is possible in the embodiments of the invention because the targets are marked with fluorescent markers.

The overlaying of the locations of early filling obtained

20 by the first marker on the real-time image showing the staining of the CNVM walls by the second marker enables identification and confirmation of the feeder vessels that contribute to the disease. These specific vessels may then be considered for laser photocoagulation treatment without

25 the massive destruction of areas of healthy vasculature and tissue.

The use of a laser that emits in the same waveband as the excitation waveband of the marker that stains the vessel

30 walls confers the further benefit of less collateral damage due to the lower laser power needed to block the stained vessels.

The "self-tracking" embodiments of the invention can be

35 likened to computerised finger-print recognition, at a basic level. It may be achieved using the following steps. The computer remembers a "map" (image) with key

(user-registered) landmarks. Upon receiving a new image (live or still), it uses that (stored) map, rotates it, scales it, or uses any (known) means to find out if the new image is the same as the map but in a different orientation

5   and/or scale. The "self-tracking" function has 2 parts:

(i) once the first (map) image is registered (in the memory) with its landmarks (e.g. where major vessels emanate from the edge of the optic disc), the software must find the same location every time (and maybe, be able to

10   move the machine to the re-oriented map position), and,

(ii) if required to zoom in on a specific area within the new image (i.e. re-scale the new image), the software must triangulate (based on the landmarks) and memorise the co-ordinates so as to zoom in, (and maybe later, zoom out

15   to the scale of previous image). It must also keep the machine pointed at the same spot during any operations.

Below are the descriptions of specific embodiments of the invention to illustrate the invention in a non-limiting

20   way.

EXAMPLE 1 - Using Threshold Triggering

A flow chart of a method of the invention is thus:-

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S1: Main Start

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S2: Fluorescein Sequence

(

30   S3: ICG Sequence

(

S4: Treatment Sequence

(

S5: PDT Sequence

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In more detail, a method of the invention is carried out as follows.

MAIN START - S1

The patient is prepared :

Measure the curvature of the cornea for the best-fitting (or the closest-fitting) contact lens to use.

5

Dilate the pupil, insert the lid retractor, etc.

Adjust the fixation light, the head-chin rest and the seat height to pose the patient in an appropriate and comfortable.

10

Insert an intravenous tap (through which the dyes can be injected) usually at the back of one hand.

FLUORESCEIN SEQUENCE - After completing S1

15   Use "general illumination" (any colour) to aim at the appropriate area, adjusting the illumination intensity, the magnification and the focus (in any order) to achieve the required field of view and details. (Illumination is adjusted to the appropriate minimum levels such that clear,

20   low-noise images can be seen, i.e. no exact magnitude can be stated as it depends on the optics and media of the machine and the human eye. The images are black and white, using grey level determination.)

25   Usually, use low magnification (and therefore wider field) to begin.

Once the general (or specific area) is in focus, change the filters to the appropriate set (blue excitation,

30   (=480-495nm; green barrier, (=515-535nm) for fluorescein.

Prepare triggering software :

Preset to capture images at the maximum frame rate (60 full frames per second because of the blood flow rate - it takes

35   10-25s after injection for the dye to arrive in the eye) for the maximum length of time permissible. (The latter is limited by the size of the computer memory).

16

Take a background scan of the image using the chosen filter
set. The image is black (if no fluorescein is present) as
the barrier filter does not pass the blue excitation
illumination.

5

Set the triggering threshold to be the background level
plus xx units. (xx is empirically established or estimated.
The units are usually grey levels. The threshold is usually
the average brightness of the entire image or the diagonal
10   strips of pixels across the image, etc - depending on the
speed of the computer, the CPU time allowed for the
averaging operations, etc. Or, any other sensitive measure
of brightness changes in an image.) Hence, the threshold is
relative to the "background" (brightness) plus xx. It does
15   not matter if the dye is already present; only the increase
in the signal (above the earlier recorded "background") is
needed threshold triggering. (See Comments below for an
alternative to threshold - triggering.)

20   Inject 3-4ml (or an appropriate dose) of fluorescein
through intravenous tap.

On the earliest appearance of the fluorescein in the field
of view (FoV - i.e. the focal plane), and at an image
25   brightness equal to or greater than the threshold, the
evolving filling of the vessels in the FoV is captured and
stored in the computer memory. Only a few (consecutive)
frames (<10), when the fluorescein signal begins to appear
and increase (in the vessels) are useful. The brightening
30   spots in these few frames suggest the location(s) of the
feeder vessels because (they are filled first). The rest
of each of these few frames should remain darker (as they
are yet to be filled at this time).
The fluorescein filling begins in the choroid (below the
35   retina). However, the Retinal Pigment Epithelium (RPE - the
pigmented layer between the choroid and the retina) blocks
(or strongly and significantly attenuates) the excitation

illumination from reaching the choroid. The RPE also blocks
the fluorescein fluorescence (if any) from the choroid. The
feeders breach the RPE to feed the associated membranes in
the sub-retina. These feeders (followed by the membranes)
5   will fill after choroid filling but before the retinal
vessels flash. The time lapse between choroidal and retinal
filling is (usually) less than 100 milliseconds. Hence,
expect a darkened image, then a sudden bright flash (as
retina vessels fill). (In contrast, the eye blink response
10   is estimated to be about 250ms.)

If the triggering sequence is correctly captured, either of
the following is expected:-
spots or lines indicating where the feeders fill, followed
15   by a spreading (fanning) out of the filling into patches in
the immediate neighbourhood of the spots or lines (feeder
vessels), or,
spots and lines fill, followed by a spreading out of the
filling, centred about the spots and lines, until the spots
20   and lines disappear in the brightening patches.

Thus, the first few consecutive frames capture the
locations of the first filling of the spots and lines that
are the suspected feeders. After that, the
25   capillaries-membranes fill - overwhelming the feeder
locations or not - then the retinal vasculature begins to
fill and the entire image is overwhelmed by a bright flash.

The captured sequence is displayed for the operator to
30   inspect in order to locate the suspected feeder(s) - the
spots and lines.

These first few (<10) frames are (image-processed to
increase image clarity, if needed, and) stored in permanent
35   memory (hard disk). The entire captured sequence can also
be saved, as required; e.g. for demonstration purposes.

18

Repeat the injection and image-capture sequence, if the previous sequence is unsatisfactory. Use another 2-3ml of fluorescein. Note that the already present fluorescein will contribute to the higher background "noise".

5

ICG SEQUENCE - After completing S1 and S2
Revert to "general illumination" and adjust the intensity, the focus and the magnification on the suspect area(s) - those determined by fluorescein early filling.

10

Change to the ICG filter set; change the illumination to infra-red (IR: (=780-790nm); barrier ((=810-880nm).

Adjust the IR illumination intensity - usually low; depends
15   on the optics, the media and the amount of ICG to be
injected.

ICG early filling is unlike the patchy fluorescein filling. Captured images have higher contrast, showing the
20   sequential filling from the choroidal to the (arterial) inflow, to the fine filling of the capillaries-membranes and to the (venous) outflow of the feeders, and lastly, to the retinal vasculature. This allows for a 2-dimensional - or a 3-dimensional reconstruction of the sequentially
25   captured images to visualise the structure - direction of vessel growth, etc - of the feeders and the capillaries-membranes.

Variation A
30   Run the software (as before for fluorescein).

Capture an ICG early filling sequence for comparison to the fluorescein sequence to confirm the location(s) of the feeders.

35

Inject 2-3ml of ICG (through the intravenous tap).

Capture the ICG early filling (as before for fluorescein).
The image is black before ICG arrival. When the ICG
arrives, there will be choroidal flash, followed by the
filling of the feeders, (spreading out from arterial to
5   venous), and lastly, the retinal filling.

Store the captured sequence or frames as required (as in
Fluorescein Sequence).

10 Variation B
Select one or a few frames from the stored, early
-fluorescein -filling.

Overlay the selected frame(s) on the "live" image (at the
15 same   magnification,   orientation,   etc).   (See
"self-tracking".)

Inject 2-3ml of ICG (through the intravenous tap).

20 Observe the ICG filling and the staining of vessels under
the superimposed (fluorescein frame).

Variation C
Inject 2-3ml of ICG (through the intravenous tap).
25

Observe and directly capture (no need to use the
trigger-capture) the inflow and the outflow of ICG through
the (particular area of the) circulation - the filling from
the arterial to the venous sides of the feeder and the
30 membranes. Can It is possible to see where and how the ICG
bolus moves through the circulation - thereby locating the
feeder (arterial) input into the membrane.

The ICG fills the vessels, then is removed from the
35 circulation. However, the ICG stains the diseased vessels
(feeders) so that as time elapses, only the ICG-stained
feeders will remain visible. Therefore, by adjusting the

illumination intensity accordingly, the non-pathological
circulation will fade out of view (in about 3-5 minutes
post-injection).

5   Feeder locations are thus confirmed.

Maintain the same filter set, adjusting IR illumination as
needed.

10   TREATMENT SEQUENCE - After completing S1, S2 and S3
Move the treatment laser aiming beam ((=633nm) to the
location of the feeder(s) - the ICG-stained spots (usually
arterial first, if they can be differentiated).

15   Adjust the treatment power and the pulse duration.
(Magnitudes are empirically established or estimated.)
Usually, start at a lower power-duration combination, then
increase until the required effect is seen on the live
image. (Usually no more than 1000mW for up to 300ms per
20   pulse is used.) Alternatively, fix the power-duration
combination but repeat the pulsing until the required
effect is seen. (The number of pulses is not fixed.)

A small amount (1-2ml) of ICG can be simultaneously
25   injected (to increase the signal and the laser absorption).

Fire the treatment laser on the targeted feeder (until the
required effect is seen, if possible). The treatment
((=810nm) laser delivers thermal (IR) energy to the target.
30   It literally burns the feeders. Hence, it is important
that the treatment spot be very concentrated (<(100(m) to
deliver a high concentration of thermal energy and to
ensure that collateral damage - damage to the neighbouring
areas about and beyond the laser spot - is minimised, i.e.
35   only the feeder is burned.

Inject a small amount (1-2ml) of ICG to look for immediate

confirmation of the treatment effect. If the treatment is
effective, the feeder is blocked and the membrane does not
fill (with ICG).

5   Depending on the FoV, the sequence may be repeated at other
areas. (See "self-tracking".)

PHOTO-DYNAMIC THERAPY

10 A sequence similar in procedure to Photo-Dynamic Therapy
(PDT) can be inserted at the end of the Treatment Sequence.

PDT uses the photo-chemical effect of a photo-sensitizer
15 chemical which concentrates or is selectively absorbed in
the pathological neo-vascular vessels. The photo-sensitizer
does not stain or only minimally concentrates in healthy
areas. The stained pathological areas are exposed to the
sensitizer's waveband at low intensities for extended
20 periods. On activation (by the illumination), the
photo-sensitizer releases singlet oxygen and/or other
highly reactive intermediates ("free radicals") which can
cause cellular damage in (the cell membranes of) the
pathological new-growth vessels, which may result in
25 thrombosis of the vessels. It has been found that PDT may
be more efficaciously applied on capillaries (in the
membranes) than on the feeders (nourishing the membranes).
It has been observed that the capillaries regrow within 12
weeks of the last PDT treatment. (U Schmidt-Erfurth,
30 ARCHIVE of OPHTHALMOLOGY, 117#9, 1177-1187, September
1999.) I broke into a new paragraph.

ICG can be analogously considered as such a
photo-sensitizer in our application. The principal
35 difference is that ICG does not release "free radicals" or
such. It operates with low a purely thermal effect. Like
PDT, the ICG is similarly exposed to power irradiation (

<50mW, for example). The value is not exactly known (depending on the staining, the optics and the ocular media).

5   The ICG excitation IR illumination is close to or can be the same as the treatment laser wavelength (or waveband). (This is because the overlap of ICG excitation and ICG fluorescence wavebands is relatively large. Each waveband, by itself, spans more than 100nm.) The difference between

10   illumination and treatment beams is that the continuous illumination is at much lower power and/or is much more diffused; while the treatment beam is much more focused (<(100(m treatment beam spot) and·at much higher pulsed powers (up to 2000mW).

15
     ICG stains the capillaries in the membrane as well as the larger feeder-vessels. At low IR power, the feeders themselves cannot be photocoagulated. (Only the above-mentioned ICG and Treatment Sequences can destroy the

20   larger feeders). However, it may be possible to destroy the membrane capillaries using this long, low-power exposure on ICG. As such, the entire ICG and Treatment Sequences is, in effect, a PDT Sequence as well (even if the PDT Sequence detailed below is not used as part of the viewing and

25   treatment procedure outline in the flowchart above). This is because the continuous, diffused, low-power, ICG-excitation, IR illumination is always present in the ICG and the Treatment sequences. Hence, depending on the duration of the ICG and the Treatment Sequences, the

30   capillaries-membranes are in effect being treated as well. (The ICG and the Treatment Sequences are meant to locate and destroy the feeders only. Note that the feeder signals may be harder to extract in the presence of nearby or overlying membranes.)

35
     If this is indeed the case, the patient may leave after this low-power exposure, i.e. the sequence may be

interrupted. After 1 to 2 weeks, the patient should be recalled for all the above sequences. If the PDT Sequence is successful, the capillaries, and therefore the membrane, do not accept (fluorescein and) ICG: they do not fill and
5   no signal is emitted. However, the larger undamaged feeders will remain and will be stained and be fluorescent. The advantage of this is that the background noise is reduced (as the once-surrounding or overlying membrane does not fluoresce). The feeders are then more easily, more exactly
10 located and more distinctly seen so that the Treatment Sequence can be more precisely applied.

In this manner, the capillaries-membranes are first destroyed as part of the procedure for locating the
15 feeders. Then, the feeders are targeted and destroyed in the follow-up.

PDT SEQUENCE - After completing S1, S2, S3 and maybe, S4
Revert to "general illumination" and adjust the intensity,
20 the focus and the magnification on suspect area(s) - those determined by fluorescein early filling images, or, broad areas without specific targets.

Change (or maintain) the filter set for ICG and infra-red
25 illumination (IR: (=780-790nm).

Adjust the IR intensity slightly higher than before (but <50mW), depending on the optics, the media and the amount to ICG to be injected.
30
Inject (up to 10ml) of ICG, if needed, (determined by patient's body weight).

Expose the suspect area to IR for extended periods (>15
35 minutes). The exact exposure duration is unknown.

Variation A

24

The PDT Sequence can be carried out after executing the ICG
and the Treatment Sequences because the diseased
capillaries-membrane are not treated - too small or too
fine, over too wide areas for the Treatment Sequence to be
5   applied. Hence, apply the PDT Sequence after the feeder
treatment to destroy the remaining capillaries-membranes.

Variation B

The PDT Sequence can be carried out before executing the
10   Treatment Sequence, especially if the feeders cannot be
clearly located because they are hidden by the overlying
capillaries-membranes. In this case, apply the PDT Sequence
to destroy the capillaries-membranes to reduce their
"noise" contribution to the image so that the underlying
15   feeders can be more clearly defined by a re-execution of
the Fluorescein and the ICG Sequences (which may be carried
out 1 or 2 weeks after the PDT Sequence).

EXAMPLE 2 - Using extensive RAM

20

Example 1 is repeated using very large (image) storage
memory as an alternative to threshold triggering. Upon
injection of any dye, the system immediately begins to
capture and store all incoming images (at 60 frames per
25   second or faster). With ample memory which provides the
needed extended period of image capturing, the early
filling is captured within 10-15s from injection. This
takes care of false triggering due to over-sensitive
threshold, or, no (or late) triggering due to overly high
30   threshold setting (i.e. xx set too large). This setup has
the added advantage of capturing any "anomalous" events
before or after the first visual appearance of the dye.
Note that the fast electronic sensor (CCD camera) can
detect "brightness" increases that are still invisible to
35   the human eye, or, that can be displayed (without
enhancement) on the monitor screen. The user will, however,
have to select those frames to be saved (on hard disk) as

saving the entire captured sequences will require too much memory (on the hard disk) and will also take too long to complete.

5   The invention thus provides methods for identifying and treating neovascularization such as in AMD.

Claims

1. A method of treating neovascularization in the eye of
5   patient comprising:-
    introducing a detectable marker into the circulation of the
    patient at a point remote from the eye;
            observing   a   region   of   suspected
            neovascularization in the eye after introducing
10   the marker;
            detecting the location of the onset of the marker
            into the region in order to determine the
            location of a feeder vessel to the region of
            neovascularization or an anomaly in the retinal
15   pigment epithelium; and
            photocoagulating the feeder vessel to prevent it
            from feeding blood to the neovascularization

2.   A method according to Claim 1, wherein the marker is
20 a fluorescent dye, the region is illuminated by radiation
    that excites the dye and the first appearance of the dye in
    the region is detected as an increase in brightness by a
    predetermined amount above background levels.

25 3.   A method according to Claim 1 or 2, for treating
    neovascularization in a Choroidal Neo-Vascular Membrane
    (CNVM) in Age-related Macular Degeneration.

4.   A method according to any of Claims 1 to 3, wherein
30 the region is observed by recording a succession of images
    of the region using an image recorder and subsequently
    examining the recorded images to identify the location of
    a blood vessel feeding blood into the region.

35 5.   A method according to Claim 4, wherein the image
    recorder captures images at a rate of at least 30 per
    second.

27

6. A method according to Claim 4 or 5, wherein recording of images of the region is triggered by trigger means associated with the image recorder and sensitive to an increase of the marker in the region.

7.   A method according to any of Claims 1 to 6, wherein the blood vessel is treated by using a laser.

8.   A method according to any of Claims 1 to 7, further comprising introducing a second detectable marker into the circulation of the patient, and detecting the location of the second detectable marker in the region so as to determine the positions of blood vessel walls in the region.

9.   A method according to Claim 8, comprising comparing the location of the first appearance of the first detectable marker into the region with the position of the blood vessel walls located by the second detectable marker to determine and/or confirm the location of a blood vessel feeding blood into the region.

10.   A method according to any of Claims 7 to 9, comprising treating the blood vessel using a laser wherein the waveband of the laser is the same as the absorption peak in the wave band of the second detectable marker.

11.   A method according to any of the preceding claims, wherein a change in brightness is measured at the location of the onset of the marker and recorded against time to facilitate determining the locations of the earliest onset of the marker into the feeder vessel.

12. A method according to claim 11, wherein the change in brightness is recorded graphically.

13. A method according to claims 4-6 wherein an image (or

images) showing the earliest appearance (of the first
marker) is made semi-transparent and then is superimposed
on the real-time image in which the second marker is
introduced, the presence of the second marker in underlying
5   locations (in real-time) indicating and confirming the
suspected feeder vessels; and absence of the second marker
in underlying locations indicating and confirming that the
suspected feeders have been coagulated successfully.

10   14. Apparatus for examination of neovascularization in an
eye of a patient, comprising:-
          a light source for exciting a dye introduced into
          the circulation of the patient;
          an image generator for generating an image of a
15   region of the eye under examination; and
          an image recorder for recording a plurality of
          images of the region.

15. Apparatus according to Claim 14, wherein the image
20   recorder can record images at a rate of at least 30 per
second.

16. Apparatus according to either of claims Claim 14 or 15,
further comprising trigger means associated with the image
25   recorder and sensitive to an increase in the brightness of
the marker in the region for triggering the image recorder
to start recording when the brightness rises above a
predetermined level.

30   17. Opthalmalogical apparatus having a lens system for
examining and treating the eye, whereby neovascularization
can be diagnosed by introducing a marker into the
circulatory system and detecting the marker in the
foveal-macular region of the eye;   the apparatus
35   comprising:
          a laser source, an illumination source and an
          image intensifier arranged on respective optical

paths of the lens system;

a high speed CCD camera coupled to the image intensifier and to a video image generating system whereby frames of image information can be captured and stored in which the onset of the marker into a feeder vessel to the choroidal neo-vascular membrane (CNVM) can be detected, so that the laser source can be used to photocoagulate the feeder and thereby treat the neovascularization.

18. Apparatus according to claim 17, wherein the lens system includes confocal imaging paths.

19. Apparatus according to claim 17 or 18 including means responsive to an increase in brightness in an image generated in the frames so as to signal the arrival of the marker in the foveal-macular region of the eye so as to trigger the image generating system to begin recording frames at a frame rate fast enough to enable the onset of the market in the feeder vessel to be determined, as well as subsequent filling of the feeder vessels, before the marker fills the visible retinal vasculature.
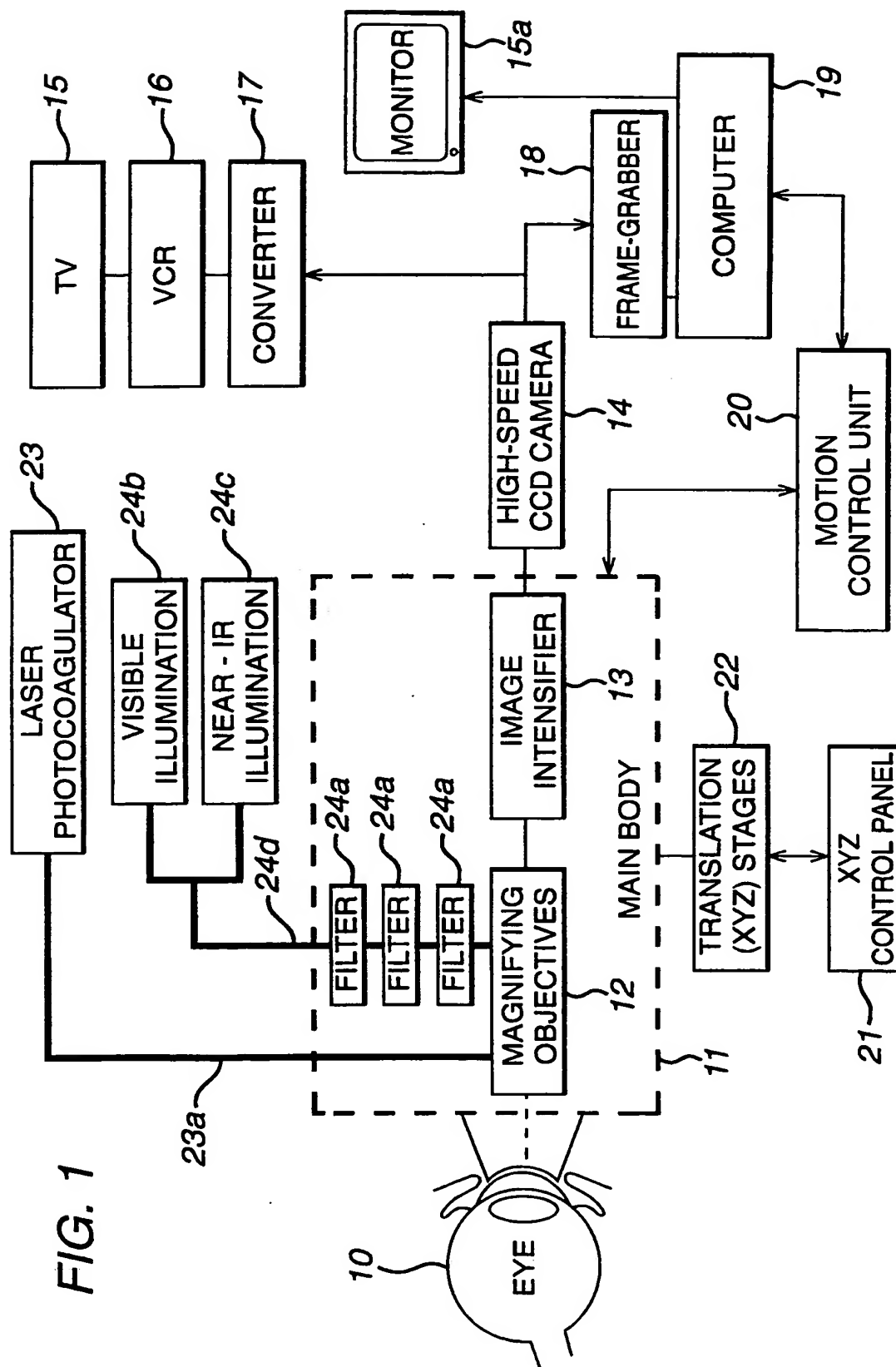
20. Apparatus according to any of claims 17- 19, wherein the marker is fluorescent and the light source emits radiation that excites the fluorescent marker.

21. Apparatus according to claim 20, wherein a second fluorescent marker is introduced into the circulation and including processing means programmed to detect the location of the second marker so as to determine the position of blood vessel walls so as to build up a map or network of the vasculature including feeder vessels, and to show an image or images of the location of the onset of the first marker against the images of the vasculature, to facilitate determining the location of the feeder vessel.
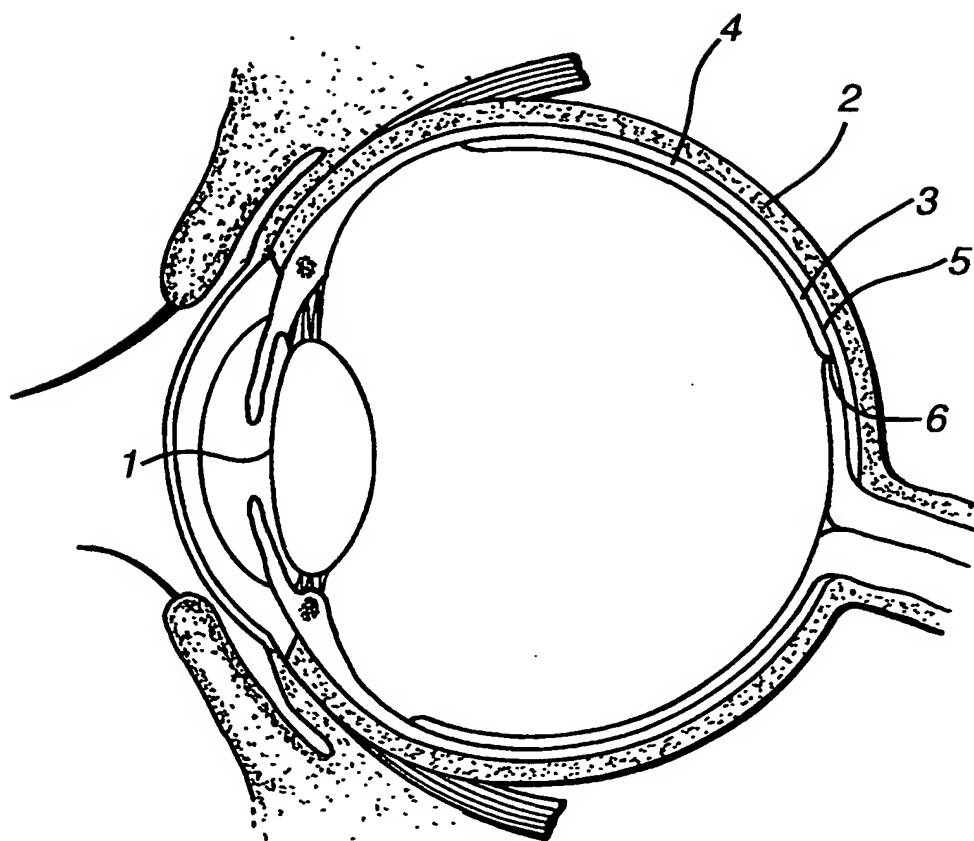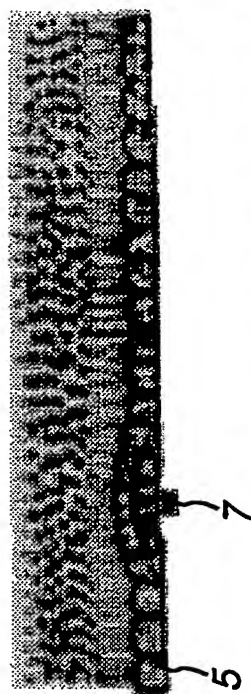
FIG. 1

FIG. 2

FIG. 4a

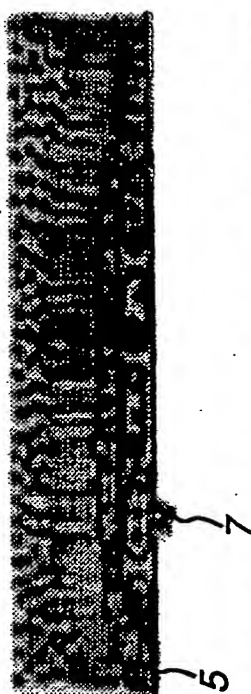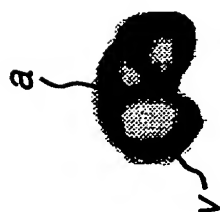FIG. 4b
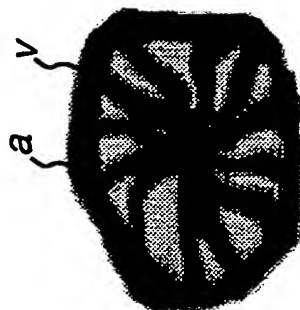
FIG. 4c

a = ARTERIAL
v = VENOUS
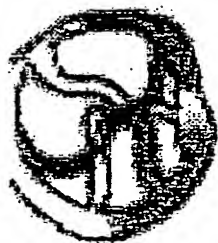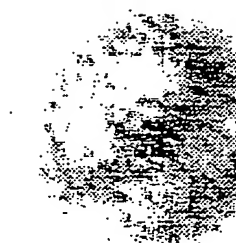
FIG. 3a

FIG. 3b

FIG. 3c

FIG. 5

$t = \frac{1}{60} s$ FIG. 5a

$\frac{2}{60} s$ FIG. 5b

$\frac{3}{60} s$ FIG. 5c

$\frac{4}{60} s$ FIG. 5d

$\frac{5}{60} s$ FIG. 5e

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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7   A61B3/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7   A61B   A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 46122 A (AVIMO EUROP LIMITED; AVIMO GROUP LIMITED (SG); PANG KIAN TIONG (SG)) 22 October 1998 (1998-10-22) cited in the application	14-20
A	page 37, line 3 - line 24 page 5, line 12 -page 6, line 9 page 7, line 19 - line 24 page 29, line 12 - line 28	21
X	WO 96 18415 A (UNIV JOHNS HOPKINS) 20 June 1996 (1996-06-20) page 19, line 16 - line 28	14,17,20
A	page 24, line 13 - line 26 page 26, line 10 -page 27, line 17 page 35, line 1 - line 16	15,21

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 June 2000	03/07/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KLINGBELL U ET AL: "LASER-BASED FUNDUS CAMERA FOR INFRARED ANGIOGRAPHY" OPTICAL ENGINEERING,US,SOC. OF PHOTO-OPTICAL INSTRUMENTATION ENGINEERS. BELLINGHAM, vol. 34, no. 3, 1 March 1995 (1995-03-01), pages 737-745, XP000495218 ISSN: 0091-3286	14
A	section "2.2 Optical Systems" section "2.4 Digital imaging System" section "4.2 Clinical Application" page 744, right-hand column, line 4 - 17	17,20,21
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A	column 4, line 35 -column 5, line 10 column 6, line 3 - line 24	21

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